THE MORPHOLOGY OF CLUBBING*

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Since antiquity certain changes in the fingers have pointed toward the probable coexistence of serious internal disease. Hippocrates[1] stressed the diagnostic importance of exaggerated curvature of the fingernails in empyema. Aretaeus,[2] in describing the crooked fingernails often found in association with chronic phthisis, attributed the nail changes to a wasting away of all the soft tissues, particularly of the distal nailbed.

According to Ebstein,[3] it was Caelius Aurelianus (*circa* 200 A.D.)[4] and not Hippocrates who first drew attention to the increase in volume of the finger tip as the important feature in clubbing. Except for the brief Hippocratic commentary references to crooked fingernails as a diagnostic sign of empyema and phthisis, there was apparently little interest in these digital changes during the subsequent years until 1832 when Pigeaux[5] published the first definitive work on clubbing.

Bamberger in 1889[6] and 1891[7] and Marie in 1890[8] discovered the presence of bone and joint changes in a few patients with marked clubbing. The latter writer named this *"osteo-arthropathie hypertrophiante pneumique,"* and sometimes hypertrophic pulmonary osteoarthropathy is referred to as "Marie's disease." Since these original descriptions of hypertrophic osteoarthropathy, there have appeared several comprehensive reviews on the subject.[3,9-19]

Clubbing and, much more infrequently, the full syndrome of hypertrophic pulmonary osteoarthropathy have been observed not only with certain types of lung disease, but also in association with cardiovascular lesions, extrathoracic abnormalities, and as a primary familial or nonfamilial disease unaccompanied by other disorders.[15] Although classically important in the diagnosis of bacterial diseases of the lungs, the development of surgical techniques for pulmonary resection has provoked more and more interest in the study of clubbing because of the frequent association of clubbing with carcinoma of the lung.

The clinical findings[3,8-19] and roentgenologic picture[12,15,17,20-23] have been thoroughly described in clubbing and hypertrophic osteoarthro-

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pathy. The histologic changes in the skeletal system have been reported in detail by Crump[24] and others.[25-29] There is, however, some lack of clarity as to the structural alterations involved in clubbing. With respect to the pathogenesis of this disease, much remains to be learned, and we are today reminded of Samuel West's comment in 1897: "Clubbing is one of those phenomena with which we are all so familiar that we appear to know more about it than we really do."[30]

Definition and Clinical Description of Clubbing

Clubbing is characterized by a bulbous enlargement of the distal segment of a digit. This digital segment may approach spherical form in marked clubbing. Toes are usually affected as well as fingers, except in cases of unilateral clubbing. But the deviations from normal in toes are more difficult to ascertain because of the effects of shoes and posture.

Lovibond[31] was the first to publicize objective measurement of the "profile sign" as the criterion for clubbing. When a nonclubbed digit is flexed at the distal interphalangeal joint, it is observed that an angle is formed by the following two lines drawn in the midsagittal plane: a line parallel to the nail at the nail base; a line resolving the surface contour of the soft tissue proximal to the nail on the dorsum of the distal phalanx. The apex of this angle normally points toward the palmar side of the digit, and the angle is equal to approximately 160°. The essential change in clubbing is an increase of this angle, approaching a straight line. In exaggerated clubbing, this angle may be greater than 180° and the point of union of nail and soft tissue at the nail base projects dorsally.

The beginning stages of clubbing can be detected by palpation at the base of the nail. In early clubbing the nail becomes more freely movable. The examiner notes a spongy sensation as though the nail is being ballotted on an edematous pad. The skin over the nail base is smooth and shining; the minute skin creases disappear. Color changes are not constant, but cyanosis of the nailbed and increased pink hue of the skin at the nail base are often observed. The process of clubbing is usually painless and so gradual as to proceed unnoticed by the patient. An exception to this is sometimes the clubbing occurring with lung carcinoma, which may be abrupt in onset and associated with pain and difficulty in moving the fingers.

Summary of Previous Descriptions of Clubbing

Pigeaux in 1832[5] wrote that blood-tinged fluid infiltrated the soft tissues under the nail and thus elevated the nail. However, he could see no changes microscopically. Several reports in the next 80

years[25,26,32-36] were remarkable chiefly in their variance with one another over the histologic description of the clubbed digit.

Grafe and Schneider (1913)[37] concluded that the chief reason for abnormal curvature of the nail was increased thickness of the nailbed. Locke reported in 1915[13] that there was some edema of the cutis and thickening of arterial walls. In 1923 Schirmer[38] reported the unique finding, in the subcutaneous tissue, of a net of fine connective tissue fibrils with a homogeneous basophilic ground substance in which many capillaries and a few infiltrations of round cells were seen. The homogeneous ground substance gave a reaction with thionine and mucicarmine in a manner consistent with mucin. Schirmer postulated that clubbing might be due to an embryonal mucinous substance replacing the adult type of subcutaneous connective tissue.

Campbell in 1924[39] published descriptions and photomicrographs of one clubbed and one normal finger. He pointed out that the essential difference between the two was edema of the tissues of the finger tip, especially in the nailbed. In 1950 Bariety and Coury[17] noted capillary dilatation and edema as the sole pathologic changes.

Lovell (1950)[40] examined 5 clubbed and 2 normal fingers fixed and stained by an intra-arterial injection technique. In the clubbed fingers the nailbed was thicker than in the normal state; this was due to an increase in connective tissue. Less obvious was the increased thickness of the fibrous capsule enclosing the pulp. In a clubbed specimen from a patient with a congenital heart disease the superficial venous plexuses were conspicuously dilated, especially in the nailbed. The injection of neoprene into the blood vessels and clearing by the Spalteholz technique showed no difference in vascular filling among 4 normal and 3 clubbed specimens.

Gall, Bennett and Bauer (1951)[29] described the pathologic features of clubbing in connection with a study of the bone and joint changes in generalized hypertrophic osteoarthropathy. It was reported that the collagen bundles in the digits were swollen. Soft tissues were infiltrated by lymphocytes and plasma cells. The periosteum showed only minimal change—a division into outer fibrous and inner cambium layers.

Schoenmackers in 1956[41] studied clubbed toes from 26 cases of cyanotic heart disease, 5 cases of mitral stenosis, and 22 controls. He confirmed the increased thickness of the nailbed. In the nailbed sections were foci of increased translucency where elastic and collagen fibers were not discernible. In some cases there were markedly congested venous sinuses. In a few specimens the glomuses showed definite enlargement.

The published reports on the structural alterations of clubbing agree in there being no change or only minimal modifications in the bony structure of the terminal phalanx. Soft tissue changes have been held responsible for the digital enlargement. Edema, increase in connective tissue, arterial hypertrophy, capillary dilatation, and mild chronic inflammation have been noted in most of the more recent publications. The need for a comprehensive study of clubbing is made apparent, however, by the contradictions in the previous descriptions and the limited number of reports. In fact, a single specimen was examined in most of the studies and (except in 3 instances) explicit reference to control material was not made.

Methods

The hands and feet of all 350 patients examined at necropsy at the Institute of Pathology of the University of Munich during a 4-month period were investigated for the presence of clubbing. The degree of clubbing, when present, was estimated in arbitrary grades I to V. Grade I denoted increase of the "profile sign" angle to between 160° and 180°. Clubbing of grade II severity existed when the nail and proximal soft tissue surface were in a straight line. In grade III the dorsal angle at the junction of the nail and soft tissue was slightly greater than 180°, but the circumference of the distal phalangeal segment was approximately equal to that of the next proximal segment. Grade IV denoted an angle greater than 180° with the ratio of the diameter of the terminal phalanx to the diameter of the proximally adjacent phalanx slightly greater than unity. In grade V there was marked protrusion of the angle formed by the nail and the soft tissue at the nail base. There was also bulbous enlargement of the finger tip so that the diameter of the terminal segment was markedly greater than that of the proximally adjacent segment.

Ten instances of clubbing were found, and 29 cases without clubbing were selected as controls. With the exception of a 7-month-old child, the controls ranged in age from 21 to 74 years (6 cases being in the third decade, 5 in the fourth, 3 in the fifth, 6 in the sixth, 7 in the seventh, and 1 in the eighth). Fourteen patients were male and 15 female. Table I lists the cases with clubbing.

The specimen obtained in each case consisted of the entire terminal segment of the left thumb, devoid only of the nail and the skin except for a longitudinal strip 0.5 cm. wide on the palmar aspect where the epidermis lay *in situ* over the entire length of the specimen. All specimens were subjected to the same treatment: fixation for 2 weeks in Müller's formalin (10 cc. of 40 per cent formalin mixed with a solution

of 2.5 gm. $K_2Cr_2O_7$ and 1 gm. Na_2SO_4 in 100 cc. of H_2O); washing; demineralization in 5 per cent HNO_3; cutting of a thin midsagittal block; neutralization in 5 per cent Na_2SO_4 solution; washing; embedding in celloidin. Midsagittal sections were cut at 15 to 20 μ. Sections from all 39 specimens were stained with hematoxylin and

TABLE I
Cases With Clubbing

Case	Age	Sex	Diagnosis	Grade of clubbing	Thickness of nailbed
1	36	F	Chronic empyema Tuberculosis Tertiary syphilis	I	2.0 mm.
2	52	M	Rheumatic heart disease (marked aortic stenosis)	I	
3	9 mo.	M	Congenital heart disease (cyanotic type)	II	1.2 mm.
4	59	M	—	II	2.5 mm.
5	33	M	Bronchiectasis Chronic pleuritis	III	2.5 mm.
6	35	M	Hodgkin's disease (pulmonary involvement)	III	3.0 mm.
7	35	M	Chronic empyema	IV	4.0 mm.
8	51	M	Marked emphysema and bronchitis (asthma) Cor pulmonale	IV	2.5 mm.
9	27	M	Bronchiectasis Brain abscess Purulent meningitis	V*	
10	38	M	Chronic lung abscess Bronchiectasis Cor pulmonale Syphilitic meningitis	V	

* With hypertrophic periostitis of tibia, fibula, radius and ulna.

eosin. In addition, microsections of the clubbed specimens and 5 controls were stained by Verhoeff's method for elastic fibers[42] and with Alcian blue for the demonstration of mucin.[43] The last named staining technique is not specific for mucin since chondroitin sulfuric acid complexes as well as mucoitin-sulfuric acid complexes combine with the dye.

RESULTS

The thickness of the nailbed varied from 1.0 to 1.7 mm. in the control specimens except for 3 cases where the thickness was 2.0 mm. from the nail to the bone. Figures 4 and 6 demonstrate another ob-

servation when the sections were viewed without the aid of a microscope. There was increased translucency in the proximal half of the nailbed with the small blood vessels standing out in bold relief. The periosteum of the nailbed was also thicker in the clubbed specimens than in the controls. However, there was no gross change in the structure of the bone and soft tissues on the palmar side of the phalanx.

Microscopically all the clubbed specimens but one showed a less dense organization of connective tissue in the proximal nailbed (Fig. 8). The collagen fibrils and cells were separated by a greater distance. The fibroblasts (Fig. 10) appeared more primitive, exhibiting large nuclei, abundant faintly basophilic cytoplasm, and long reticular processes. The overall scarcity of formed elements with large fibroblasts set in a reticular network was most characteristic of the regions of translucency noted on gross examination, but this appearance extended to the distal portion of the nailbed. Here there was increased widening of the interfascicular spaces even in places where there were thick, dense collagen fibers.

In most of the clubbed specimens there were more lymphocytes scattered extravascularly through the nailbed than in the controls. In clubbed specimens from cases 7 (Fig. 11) and 9 there were focal perivascular accumulations of lymphocytes. In half the cases there was a moderate increase in the number of tissue eosinophils. It is noteworthy that the increased numbers of lymphocytes and eosinophils occurred only in the nailbed and not in the soft tissues on the palmar side of the phalanx.

The periosteum of the nailbed was thickened in the more severely clubbed specimens. Penetrating deep into the periosteum were small blood vessels immediately encompassed by loose reticular tissue. Extravascular lymphocytes were observed in these projections. Four of the cases with clubbing demonstrated an abnormality in the periosteum on the palmar side of the bone. One or two small collections of loosely textured connective tissue similar to that of the nailbed were found between the cambium and fibrous layers of the palmar periosteum (Fig. 12).

The arteries in the nailbed were of larger size than those in the controls, but the increase in size appeared only commensurate with the increase in soft tissue of the nailbed. In sections from clubbed cases 4 and 7 there was glomus formation throughout the length of the nailbed. The vessels, appearing to be arteriovenous anastomotic units,[44,45] were of increased caliber and number (Fig. 14). The vascular elements within a section of a glomus were also more widely separated because of the widening of the interstitial spaces.

The specimen from clubbed case 8 (Fig. 5) was an exception to

the pattern evident in the other specimens. The corium of the palmar aspect was increased approximately 0.5 mm. in thickness when compared to the other clubbed specimens and controls. This increase in thickness was caused by the presence of an abnormally thick, dense mat of collagen fibers. Other abnormalities were restricted to the nailbed. In this region there was no widening of the interfascicular spaces. The connective tissue was very compactly organized. The entire nailbed had increased collagen deposition. The vascular components of the glomuses were thick-walled and encased in a thickened fibrous sheet. There was no increase in the number of extravascular lymphocytes or eosinophils.

Table II summarizes the individual observations and shows the rather good correlation among increased thickness of the nailbed, extent of interstitial edema of the nailbed, and the clinical grade of clubbing.

TABLE II

The Anatomic Changes in Clubbing

		Nailbed					Periosteum
Case	Grade of clubbing	Increased thickness	Edema	Increased no. of lymphocytes	Increased no. of eosinophils	Increased no. coils A-V anastomoses	Nailbed-type tissue on palmar side
1*	I	+	+	+	+	o	o
2	I	+	+	o	o	o	o
3	II	+	+	o	o	o	o
4	II	+	+	†	o	+	o
5	III	+	++	+	+	o	+
6	III	++	++	+	++	o	+
7	IV	+++	+++	+++	o	++	o
8‡	IV	+	o	o	o	o	o
9	V	+++	+++	+++	+	o	+
10	V	§	+++	+	+	o	+

* Endostosis.

† Accumulations of lymphoblasts.

‡ Dense collagen in nailbed, palmar corium, fatty tissue septa.

§ Part of nailbed was inadvertently removed.

Few controls showed the abnormalities described in the clubbed specimens. Increased thickness (to 2.0 mm.) and looseness of texture of the nailbed with widened interfascicular spaces and large fibroblasts in a fibrillar network were present in the case of a 29-year-old female with sarcoma in the mediastinum and bilateral pulmonary infiltrations. The microscopic structure of the nailbed was similar to that in clubbing of grade I severity. No control possessed the loosely textured tissue on the palmar side of the phalanx described in clubbed cases 5, 6, 9 and 10, or any increase in number and size of arterio-

venous connections in the plane of the section as in clubbed cases 4 and 7. A moderate increase in the number of diffusely distributed extravascular lymphocytes in the nailbed was observed in a 40-year-old male with carcinoma of the stomach. There was also a slight increase in the number of tissue eosinophils scattered through the proximal half of the nailbed in the specimens from the following controls: a 27-year-old male with chronic caseous pulmonary tuberculosis and chronic empyema; a 30-year-old female with thrombocytopenic purpura secondary to aminopyrine sensitivity; and a 51-year-old male with complications of arteriosclerotic coronary artery disease.

Since there have been several reports attributing the changes in clubbing to hypertrophy or edema of all the soft tissues of the digit, 2 cases were studied in which each of these changes was observed upon gross examination. Specimens from two manual laborers with digital hypertrophy showed neither increased thickness nor microscopic abnormality of the nailbed. In one of these (Fig. 2) there was increased thickness of collagen in the palmar corium and some displacement of the fatty tissue by dense connective tissue on the palmar side of the distal phalanx; in the other, the hypertrophy was due to increase of all tissue components without distortion in the pattern of arrangement except for hyperkeratosis.

Of 2 cases with generalized anasarca including edema of the digits, one had nailbed thickness of 2.0 mm. with the only microscopic abnormality being swelling of the collagen bundles in the septa of the fatty tissue layer on the palmar side of the phalanx. In the other (Fig. 3) the nailbed was 1.7 mm. thick. There was a slight increase in the width of the interfascicular spaces of the nailbed, but the large fibroblasts of the clubbed specimens were lacking.

The stain for elastic tissue confirmed the findings made with hematoxylin and eosin: there was no change in the distribution of elastic fibers. The clubbed specimens and all 5 of the controls tested gave the same reaction when subjected to the Alcian blue staining technique for the demonstration of mucin and chondroitin. The articular cartilage at the interphalangeal joint was stained, the intensity varying inversely with the distance from the joint cavity. Bone showed no affinity for the dye. The soft tissues combined minimally and uniformly with the stain.

Discussion

Changes in the nailbed were responsible for the alteration in size and configuration of the clubbed digit in this study. Increased thickness of the nailbed was noted in every case. Clubbing was present

when the thickness of the nailbed exceeded 2.0 mm. This thickness was due largely to interstitial edema in all but one case. Increase in extravascular lymphocytes was observed in the majority of cases; in 2 cases there were several dense aggregations of these cells. Increase in the number of tissue eosinophils was more inconstant and less striking. The periosteum on the palmar side of several clubbed specimens exhibited a prevalence of the loose-textured connective tissue characteristic of the nailbed.

The alteration in the glomeral pattern of the nailbed in cases 4 and 7 was of particular interest. In the plane of the section there were more arteriovenous anastomotic units transected than in the control specimens. Comparison of Figures 13 and 14 illustrates this abnormality. Unfortunately, it was impossible from the material at hand to quantitate this observation adequately. It was quite evident on study of the sections that, as Popoff[44] has emphasized, the glomuses are most numerous in a plane parallel to the skin or nail surface. In a random section perpendicular to this plane, however, the sampling error does not permit valid conclusions from the present study other than to note that glomeral patterns in 2 cases of clubbing suggested increased number and size of the arteriovenous connecting vessels. The glomeral structure warrants further study, utilizing sections made tangential to the nail and skin surfaces.

Case 8 showed a more chronic form of clubbing. In this stage, edema did not appear to be part of the lesion. Cellular infiltrations were also absent. Increase in volume was due to increased deposition of dense collagen in the nailbed, palmar corium, and fatty tissue septa.

That the digital changes in clubbing are different from those seen with generalized edema of the hands or hypertrophy associated with hard manual labor is evident. The localization of the interstitial edema to the nailbed, and the other changes noted are unique to the disorder of acute clubbing. The questions arise: Why are the changes found in this site? What is the factor or combination of factors causing the predilective involvement of the nailbed in clubbing?

The proximal portion of the nailbed is metabolically active in the elaboration of the fingernail. Another noteworthy characteristic of the nailbed is the abundance of glomus formation in this tissue.[44,45] It has been reported that the number of anastomoses per square centimeter of surface area in one digit studied was 510 in the nailbed, 236 at the finger tip, and 150 in the palmar tissue of the distal phalanx.[45]

It was particularly interesting to note in the thickened periosteum of the phalanx, interfascicular edema and small collections of the same type of loosely arranged connective tissue encountered in the nailbed.

Crump[24] described regions containing sparse cells and fibrils in the periosteum of bones showing hypertrophic periostitis. An increase in cells with oxyphilic granules was noted in some of these foci. Gall and co-workers[29] described edema as a prominent feature of the early periosteal change associated with subperiosteal new bone formation. Of importance is this morphologic similarity of the periosteum in the process of clubbing and in hypertrophic periostitis.

Theories of Pathogenesis

There is an abundance of speculation concerning mechanisms of clubbing in previous publications. Many reviews provide lengthy theoretical discussions which do not require repetition. Certain recent developments, however, merit attention.

One of the handicaps in the study of the pathogenesis of clubbing and hypertrophic periostitis, despite numerous attempts to produce this pathologic state experimentally, is the dearth of positive results.[7,46-51] Mendlowitz and Leslie[48] anastomosed the left pulmonary artery and left atrium in the dog, producing a right-to-left shunt with corresponding desaturation of systemic arterial blood. It was shown that in addition to cyanosis these dogs had an increase of cardiac output after the shunting procedure. One dog so treated developed minimal but demonstrable changes of hypertrophic periostitis on certain long bones.

The influence of certain surgical procedures on soft tissue, bone and joint changes in hypertrophic osteoarthropathy associated with carcinoma of the lung has been reported recently. Excision of the affected pulmonary tissue,[19] ligation of the pulmonary artery,[52] section of the nerve branches at the hilus,[53,54] and severing of the vagus nerve just below the recurrent laryngeal nerve[55] on the affected side, have all been reported as bringing about prompt and dramatic remission of the peripheral signs and symptoms.

Mendlowitz[18] has recently summarized his studies on the abnormal physiology of the digital circulation in clubbing. He has found by calorimetric measurement that acquired symmetrical clubbing is usually associated with increased blood flow in the finger tips, this increase in blood flow being out of proportion to the increase in soft tissue mass. Mendlowitz[18,56] has propounded the theory that in clubbing there is an increase in pulmonary circulation without a corresponding increase in the demand for blood in the systemic circulation. This produces a local oversupply of blood to the fingers and toes, and—in cases of osseous involvement—to the affected bones. Questions unanswered by this theory are: (1) What causes this increase in pul-

monary circulation, if it does exist? (2) What is the mechanism whereby digital blood flow is increased? The function of the arteriovenous anastomoses in the glomuses is presumably involved, but how is this effected?

Summary and Conclusions

Midsagittal sections of the thumb from 10 cases of clubbing and 29 nonclubbed control specimens were examined. The alteration in shape of the digit in clubbing resulted from an increase in thickness of the nailbed. In the series of cases studied, a thickness of the nailbed of the thumb greater than 2.0 mm. was found only in clubbed digits. The nailbed was loosely textured with large primitive-appearing fibroblasts in a wide-meshed reticular network. There was often an increased number of extravascular lymphocytes and eosinophils. In 2 cases the glomeral structure in the nailbed was altered, with more coils of arteriovenous anastomoses than usual. Severely clubbed specimens commonly showed foci of tissue in the periosteum on the palmar side which resembled the tissue in the nailbed. In addition there were edema and thickening of the periosteum. Review of the histologic observations of hypertrophic periostitis in previous writings revealed that in the periosteum overlying altered bone there had been reported focal edema and loose-textured connective tissue similar to that seen in the nailbed in this study.

In one case of chronic clubbing no evidence of edema was seen. The increased thickness was due to increased collagen deposition in the nailbed and corium of the palm.

Further study of the subungual glomus in clubbing is indicated. The similarity of the periosteal lesions in clubbing and hypertrophic osteoarthropathy points toward a similarity in pathogenesis. The new formation of bone observed in the long bones in the latter condition, however, has not been observed in the nailbed in simple clubbing.

References

1. Hippocrates. The Book of Prognostics. In: The Genuine Works of Hippocrates, Adams, F. (trans.). The Sydenham Society, London, 1849, Vol. 1, p. 249.

2. Aretaeus. On the Causes and Symptoms of Chronic Diseases. In: The Extant Works of Aretaeus, the Cappadocian, Adams, F. (trans.). The Sydenham Society, London, 1856, Book 1, Chapt. 8, p. 311.

3. Ebstein, E. Zur klinischen Geschichte und Bedeutung der Trommelschlägelfinger. *Deutsches Arch. klin. Med.*, 1906, 89, 67–112.

4. Caelius Aurelianus. On Chronic Diseases. In: On Acute Diseases and On Chronic Diseases, Drabkin, I. E. (ed. and trans.). Univ. of Chicago Press, Chicago, 1950, Book 2, sect. 14, p. 697.

5. Pigeaux, J. Recherches nouvelles sur l'étiologie, la symptomatologie et le mécanisme du développement fusiforme de l'extrémité des doigts. *Arch. gén. méd.*, 1832, 29, 174–184.

6. Bamberger, E. Verhandlungen ärtzlicher Gesellschaften und Vereine. Protokol der k.k. Gesellschaft der Aerzte in Wien. *Wien klin Wchnschr.*, 1889, 2, 225–226.

7. Bamberger, E. Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten. *Ztschr. klin. Med.*, 1891, 18, 193–217.

8. Marie, P. De l'ostéo-arthropathie hypertrophiante pneumique. *Rev. de méd., Paris*, 1890, 10, 1–36.

9. Thayer, W. S. Hypertrophic pulmonary osteoarthropathy and acromegaly. A clinical lecture, with the histories and photographs of four cases. *New York M. J.*, 1896, 63, 33–41.

10. Walters, R. F. Osteo-arthropathy and its relationships. *St. Thomas Rep.*, 1897, 24, 1–73.

11. Janeway, T. C. Hypertrophic osteoarthropathy: with report of two cases. *Am. J. M. Sc.*, 1903, 126, 563–581.

12. Alexander, J. F. Hypertrophic pulmonary osteo-arthropathy. *St. Barth. Hosp. Rep.*, 1907, 42, 41–79.

13. Locke, E. A. Secondary hypertrophic osteo-arthropathy and its relation to simple club-fingers. *Arch. Int. Med.*, 1915, 15, 659–713.

14. Högler, F. Ueber Akropachie. (Trommelschlägelfinger und Osteoarthropathie.) *Wien. Arch. f. inn. Med.*, 1920, 1, 35–76.

15. Mendlowitz, M. Clubbing and hypertrophic osteoarthropathy. *Medicine*, 1942, 21, 269–306.

16. Branwood, A. W. Clubbing of the fingers. *Edinburgh M. J.*, 1949, 56, 105–120.

17. Bariety, M., and Coury, C. L'ostéo-arthropathie hypertrophiante pneumique et les dysacromélies d'origine thoracique. Aspects anatomo-cliniques et évolutifs (à propos de 25 cas). *Semaine hôp. Paris*, 1950, 26, 1681–1708.

18. Mendlowitz, M. The Digital Circulation. Grune & Stratton, New York, 1954, pp. 114–126.

19. Semple, T., and McCluskie, R. A. Generalized hypertrophic osteoarthropathy in association with bronchial carcinoma. A review, based on 24 cases. *Brit. M. J.*, 1955, 1, 754–759.

20. Fraenkel, E. Ueber allgemeine Periostitis hyperplastica (Osteo-arthropathie hypertrophiante pneumique). *Fortschr. Geb. Röntgenstrahlen*, 1918, 25, 401–420.

21. Israelski, M., and Pollack, H. Beitrag zur Osteoarthropathie hypertrophiante nach Pierre Marie beziehungsweise toxigenen Osteoperiostitis ossificans nach Sternberg. *Röntgenpraxis*, 1930, 2, 342–352.

22. Kühne, K., and Gerstel, G. Klinisch-röntgenologische und pathologisch-histologische Befunde bei einem Fall von allgemeiner Osteophytose (Ostéo-arthropathie hypertrophiante pneumique). *Fortschr. Geb. Röntgenstrahlen*, 1932, 46, 662–670.

23. Rypins, E. L. Hypertrophic osteo-arthropathy. *Radiology*, 1935, 25, 289–294.

24. Crump, C. Histologie der allgemeinen Osteophytose. (Ostéoarthropathie hypertrophiante pneumique.) *Virchows Arch. path. Anat.*, 1929, 271, 467–511.

25. Arnold, J. Acromegalie, Pachyacrie oder Ostitis? Ein anatomischer Bericht über den Fall Hagner. *Beitr. path. Anat.*, 1891, 10, 1–80.

26. Freytag, A. Über die Trommelschlägelfinger und Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten. Dissertation, Bonn, 1891. Cited by Ebstein, E.[3]

27. Weber, F. P. The histology of the new bone-formation in a case of pulmonary hypertrophic osteo-arthropathy. *Proc. Roy. Soc. Med.*, 1909, 2 (Path. Sect.), 187–192.

28. Konschegg, T. Über die Bamberger-Mariesche Krankheit. *Virchows Arch. path. Anat.*, 1929, 271, 164–172.

29. Gall, E. A.; Bennett, G. A., and Bauer, W. Generalized hypertrophic osteo-arthropathy; a pathologic study of seven cases. *Am. J. Path.*, 1951, 27, 349–381.

30. West, S. Two cases of clubbing of the fingers developing within a fortnight and four weeks respectively, with remarks. *Tr. Clin. Soc. Lond.*, 1897, 30, 60–64.

31. Lovibond, J. L. Diagnosis of clubbed fingers. *Lancet*, 1938, 1, 363–364.

32. Simon, C. G. T. Die Hautkrankheiten durch anatomische Untersuchungen erläutert. G. Reimer, Berlin, 1851, ed. 2, pp. 399–400.

33. Fischer, H. Mittheilungen aus der königlichen chirurgischen Klinik zu Breslau. Der Riesenwuchs. *Deutsche Ztschr. f. Chir.*, 1879–80, 12, 1–59.

34. Moore, N. Congenital disease of heart. *Tr. Path. Soc. Lond.*, 1884–5, 36, 176–178.

35. Buzzard, E. F. Sequel to a case of pulmonary hypertrophic osteo-arthropathy: necropsy. *Brit. M. J.*, 1901, 1, 1333–1334.

36. Ferrio, L. A proposito delle dita ippocratiche e dei rapporti di queste coll'-osteoartropatia ipertrofizzante pneumica di P. Marie. *Morgagni*, 1902, 44, 453–471.

37. Grafe, E., and Schneider, P. Zur Kenntnis der sekundären hyperplastisch-porotischen Osteoperiostitis. *Beitr. path. Anat.*, 1913, 56, 231–265.

38. Schirmer, O. Beitrag zur Kenntnis der Akropachie. (Osteoarthropathie hypertrophiante pneumique.) *Wien. Arch. f. inn. Med.*, 1923, 5, 345–352.

39. Campbell, D. The Hippocratic fingers. *Brit. M. J.*, 1924, 1, 145–147.

40. Lovell, R. R. H. Observations on the structure of clubbed fingers. *Clin. Sc.*, 1950, 9, 299–321.

41. Schoenmackers, J. Trommelschlegelfinger und -zehen bei angeborenen Herz- und Gefässfehlern mit Blausucht. *Arch. Kreislaufforsch.*, 1956, 24, 363–377.

42. Verhoeff, F. H. Some new staining methods of wide applicability. Including a rapid differential stain for elastic tissue. *J. A. M. A.*, 1908, 50, 876–877.

43. Steedman, H. F. Alcian blue 8GS: a new stain for mucin. *Quart. J. Micr. Sc.*, 1950, 91, 477–479.

44. Popoff, N. W. The digital vascular system; with reference to the state of glomus in inflammation, arteriosclerotic gangrene, diabetic gangrene, thrombo-angiitis obliterans and supernumerary digits in man. *Arch. Path.*, 1934, 18, 295–330.

45. Grant, R. T., and Bland, E. F. Observations on arteriovenous anastomoses in human skin and in the bird's foot with special reference to the reaction to cold. *Heart*, 1929–31, 15, 385–407.

46. Phemister, D. B. Chronic lung abscess with pulmonary hypertrophic osteoarthropathy. *Surgical Clin. Chicago,* 1917, 1, 381–389.

47. Compere, E. L.; Adams, W. E., and Compere, C. L. Generalized hypertrophic pulmonary osteoarthropathy; an experimental and clinical study with report of two cases. *Surg., Gynec. & Obst.,* 1935, 61, 312–323.

48. Mendlowitz, M., and Leslie, A. The experimental simulation in the dog of the cyanosis and hypertrophic osteoarthropathy which are associated with congenital heart disease. *Am. Heart J.,* 1942, 24, 141–152.

49. Mantoux, G. L'ostéopathie hypertrophiante pneumique dans les tumeurs pulmonaires. *Semaine hôp. Paris,* 1948, 24, 2018–2021.

50. Thiers, H.; Berard; Plauchu, and Haour. Dystrophies de natures diverses chez le cobaye en voie de croissance traité par les extraits d'un cancer provocateur chez l'homme d'une ostéopathie hypertrophiante pneumique de Pierre Marie. *Rev. d. rhumat., Paris,* 1951, 18, 295–299.

51. Thiers, H.; Berard; Plauchu; Haour, and Potton. Étude histologique des dystrophies des os des parties molles et du système génital du jeune cobaye traité par des extraits d'un cancer bronchiolaire provocateur chez l'homme d'une ostéoarthropathie hypertrophiante pneumique de Pierre Marie. *Rev. d. rhumat., Paris,* 1952, 19, 532–539.

52. Wyburn-Mason, R. Bronchial carcinoma presenting as polyneuritis. *Lancet,* 1948, 1, 203–206.

53. Brea, M. M. Bronchial Adenocarcinoma and the Bamberger-Marie Syndrome. In: The 1948 Year Book of General Surgery, Graham, E. A. (ed.). The Year Book Publishers, Inc., Chicago, 1949, p. 307.

54. Hansen, J. L. Bronchial carcinoma presenting as arthralgia. *Acta med. scandinav.,* 1952, Suppl. 266, 467–472.

55. Flavell, G. Reversal of pulmonary hypertrophic osteoarthropathy by vagotomy. *Lancet,* 1956, 1, 260–262.

56. Mendlowitz, M. Cardiovascular shunts. *Am. J. Med.,* 1957, 22, 1–4.

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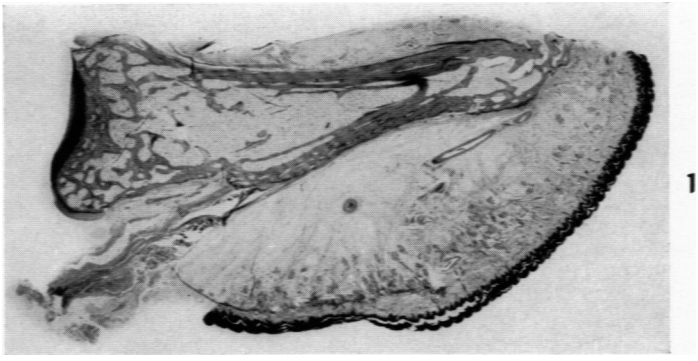
LEGENDS FOR FIGURES

All photographs are of sections stained with hematoxylin and eosin.

FIG. 1. Midsagittal section through the terminal phalanx of the left thumb from a nonclubbed control. Forty-year-old male with carcinoma of the stomach, and metastasis. × 3.

FIG. 2. Nonclubbed thumb from a 43-year-old male manual laborer who died with periportal fibrosis of the liver and ruptured esophageal varices. Thumb shows hypertrophy of all tissue components. × 3.

FIG. 3. Grossly edematous thumb from a 61-year-old female with edema of all extremities secondary to starvation hypoproteinemia. Except for osteoporosis, there is essentially no variation in the section from the other control cases. × 3.



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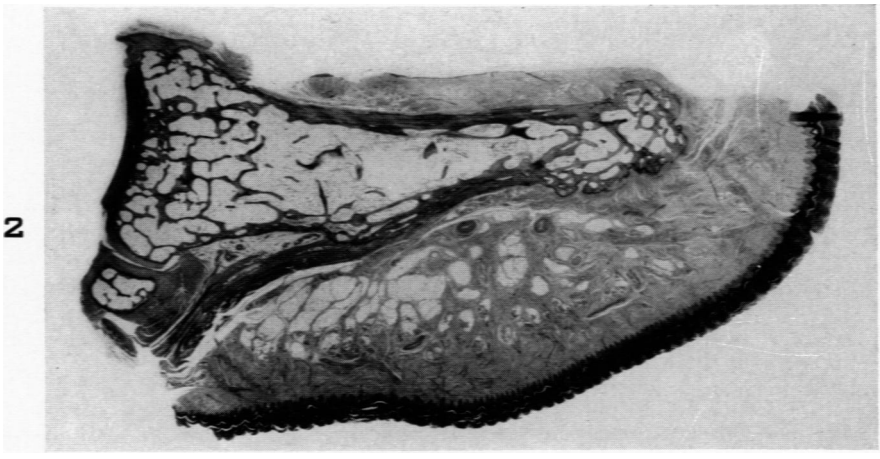

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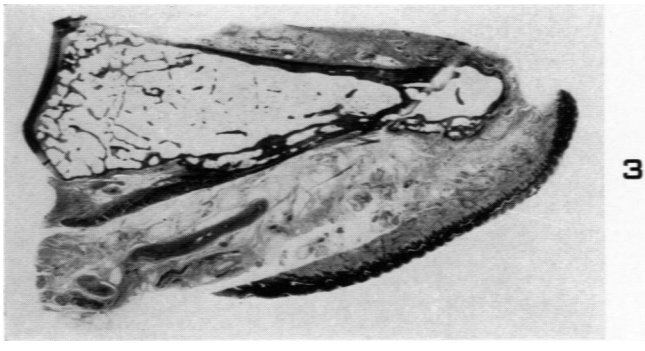

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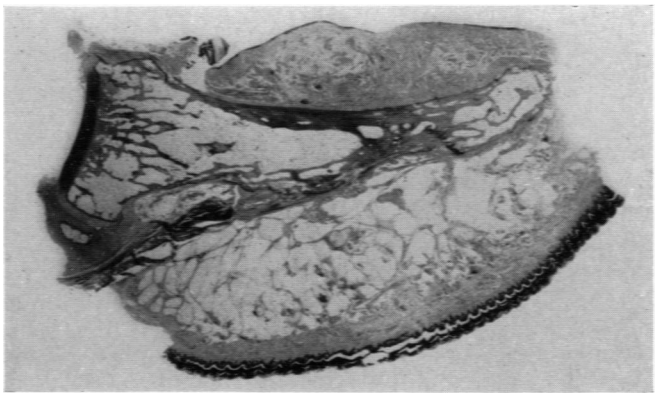
FIG. 4. Thumb from case 7. grade IV severity of clubbing. Thirty-five-year-old male with chronic empyema. Note marked increase in thickness of nailbed, increased vascularity and increased translucency of proximal nailbed. × 3.

FIG. 5. Case 8, grade IV clubbing. Fifty-one-year-old male with long history of asthma. Necropsy examination showed marked emphysema and bronchitis, chronic cor pulmonale. Midsagittal section of thumb reveals increased thickness and density of nailbed. There is increased thickness of dense connective tissue subcutaneously and of fibrous septa in fatty tissue layer on palmar side of the bone. × 3.

FIG. 6. Case 9, grade V clubbing. Twenty-seven-year-old male with bronchiectasis. Changes present are increased thickness of nailbed, decreased density and increased vascularity of proximal and middle portions of nailbed. Small region of tissue similar to that of the nailbed is seen in palmar periosteum at junction of middle with distal third of phalanx. × 3.



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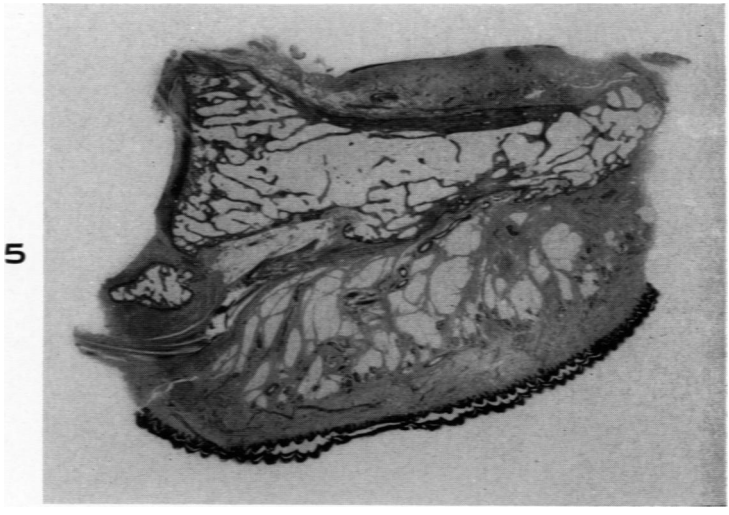

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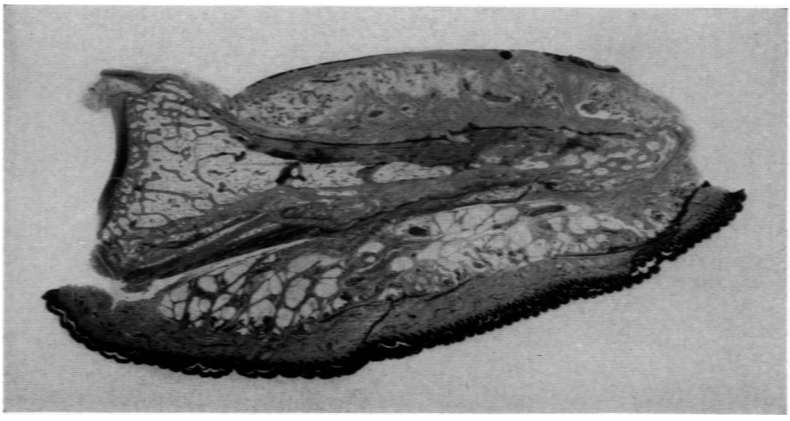

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FIG. 7. Midsagittal section of thumb (control specimen) from a 32-year-old female who died with chronic glomerulonephritis. Middle portion of nailbed with bone on the left. × 72.

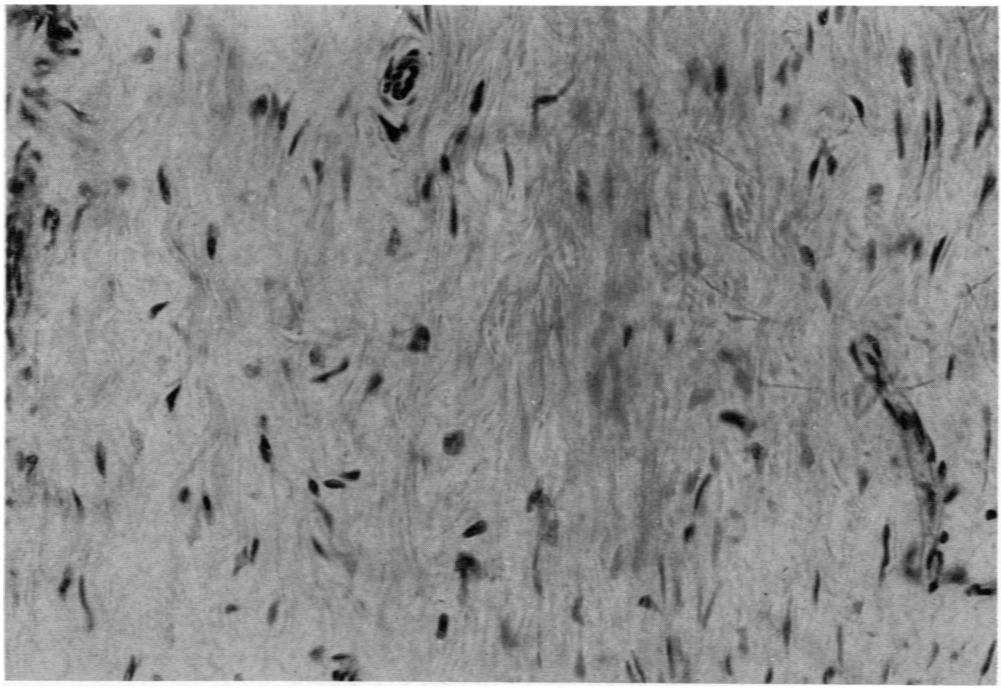
FIG. 8. Clubbed case 7. Middle portion of nailbed with periosteum out of view to left. Apparent are the increased thickness of the nailbed, relative hypocellularity, widening of the interstitial spaces, and—in the center of the picture—the large fibroblasts. × 72.

7

8

FIG. 9. Higher magnification of Figure 7. Nonclubbed control. × 300.

FIG. 10. Higher magnification of Figure 8. Decreased tissue density, widened interfascicular spaces, large primitive-appearing fibroblasts, dearth of mature fibrocytes, reticular type of connective tissue fiber, and the increased number of extravascular lymphocytes are characteristic of marked clubbing. × 300.



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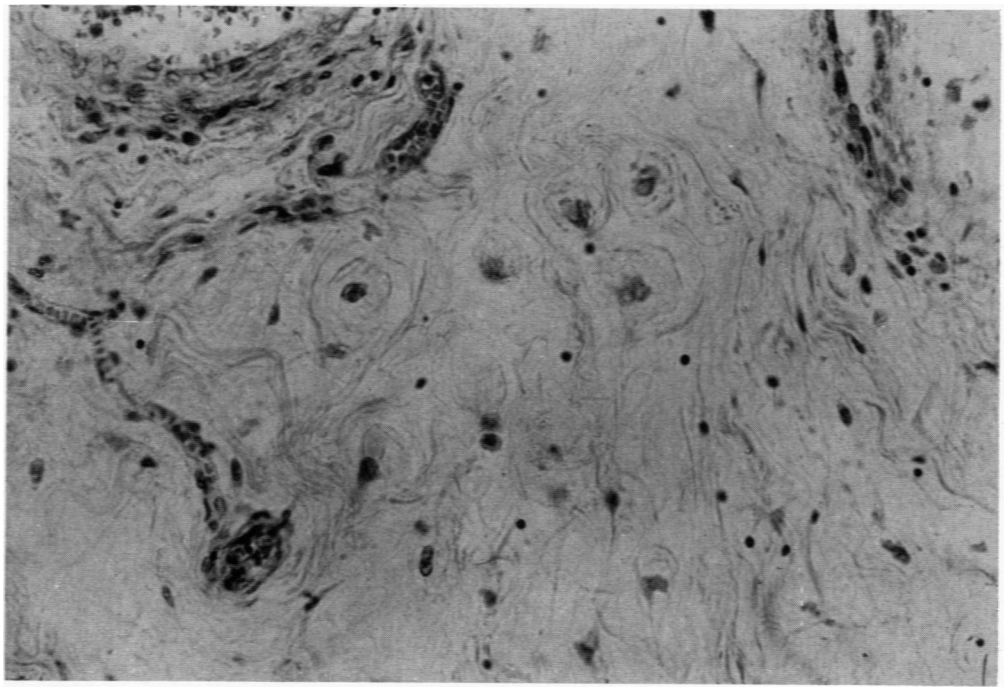

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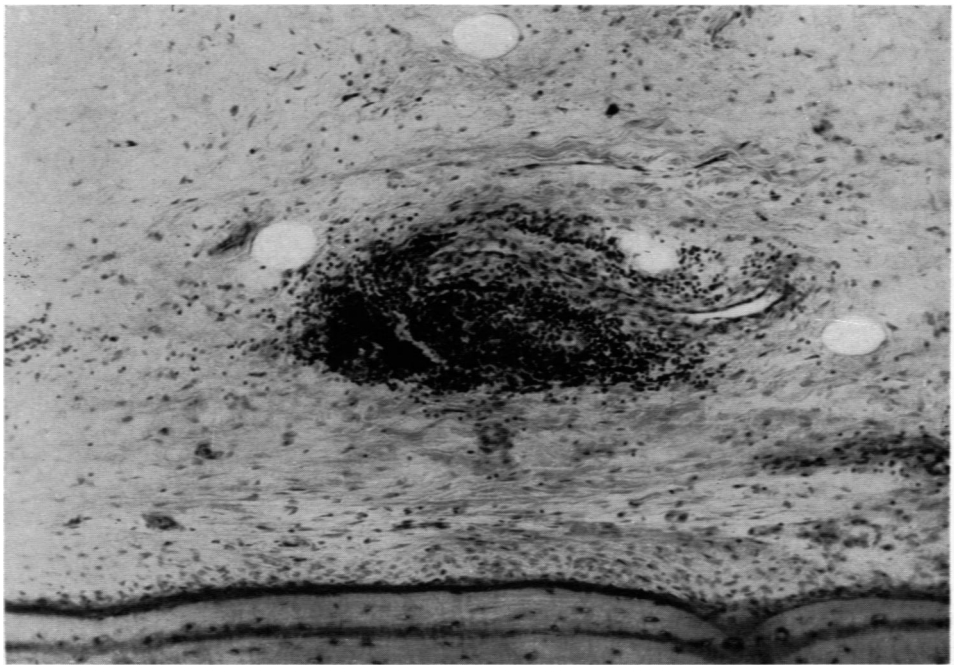
FIG. 11. Clubbed case 7. Periosteum of nailbed with bone in lower part of picture. Dense perivascular accumulation of lymphocytes is seen. × 120.

FIG. 12. Clubbed case 9, bone above. Loose tissue with widened interstitial spaces and vascularization noted in periosteum of palmar aspect of phalanx. Reference to Figure 6 will enable one to locate region in midsagittal section of thumb from which this highly magnified view is obtained. × 120.



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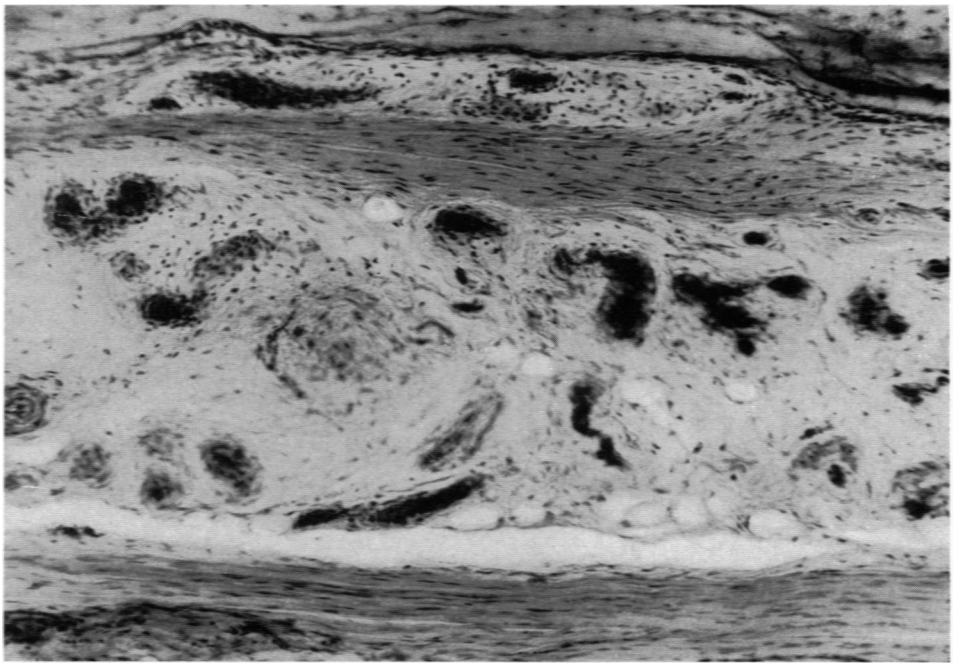

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FIG. 13. Nonclubbed control, as in Figures 7 and 9. Glomus in distal portion of nailbed with bone inferiorly. Artery courses distally from left to right. Ramifications of artery are seen at right center. Glomus is composed of nutrient arterioles, collecting veins, nerve fibers, and a major artery which divides to form smaller arteries and arteriovenous anastomoses. The glomus in this illustration is the largest encountered in all the slides of the 29 control cases. × 72.

FIG. 14. Clubbed case 7. Region in middle portion of nailbed showing microscopic alteration in vascular pattern. An artery is on the right; the rest of the photograph is filled by whorls of vessels appearing to be arteriovenous anastomotic units. × 72.

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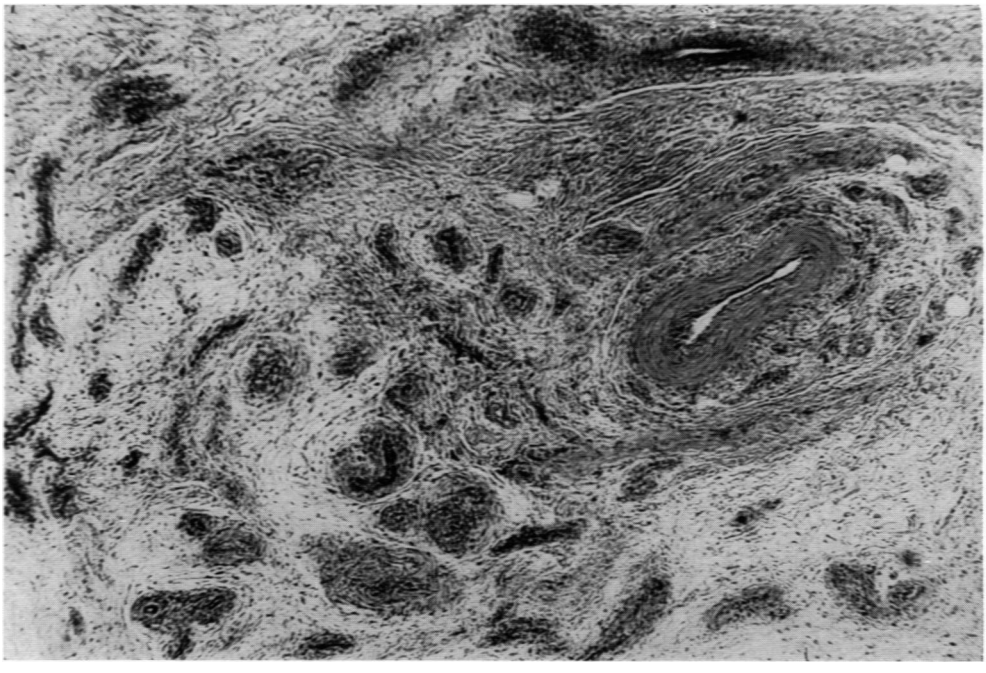

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